Diez Roux responses

REA

Chapter 5

6. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded population-based exposure analysis to be technically sound, appropriately balanced, and clearly communicated?

Overall I found the methods to be clearly presented. Figure 5-1 was especially useful in summarizing the various inputs to the modeling process. The document does a very good job of describing the various sources of data that went into the modeling process and how the data were used.

I also found the description of the model output useful, although some relatively minor editing would improve clarity. For example, the title of Figure 5-2 says "Percent of asthmatic school-age children in all study areas with at least one O3 exposure at of above 60ppb-8 hour while at moderate or greater exertion…" . It is not clear what "one O3 exposure" means in this context. Does it mean that they were engaging in moderate of greater exertion at any time during an 8 hour period with an average of >=60ppb? In order to count as "one exposure" is there a minimum time requirement (for example, must they be engaging in moderate or greater exertion during a least one hour at any time during the 8 hour averaging period?) Perhaps I am misinterpreting the output measure reported here, if so this needs to be clarified.

Figure 5-3 was very helpful as a way to present the results but a bit more clarity in the labeling would help readers better interpret the graphics. For example the labeling of the bottom panel could be "Percent of asthmatic school age children with at least one exposure [see my note above regarding clarifying this metric] at or above 60ppb, 70 ppb and 80 ppb (red, green and blue lines) when air quality was adjusted to just meet standards of 75, 70. 65 and 60 ppb (panels left to right).

Section 5.3.3 provides a very good description of the results. A summary at the end of the section highlighting the key points (especially those that will be of relevance to the PA) would be very helpful.

7. Chapter 5 includes several evaluations of key APEX inputs and model outputs, including for example analysis of time-activity data and comparison of actual personal exposures with modeled exposures. What are the views of the Panel on the appropriateness and usefulness of these evaluations and the conclusions drawn from these evaluations?

I found the evaluations presented in section 5.4.1 useful and well described and the conclusions reasonable. The document has been greatly strengthened through the

incorporation of this section. Section 5.4.4 was also useful although the lack of agreement wit the Detroit data in section 5.4.4.1 needs to be explained or at least further discussed with respect to the implications of this for the exposure estimates previously presented.

8. Chapter 5 includes several scenario-based exposure simulations that focus on specific populations or behaviors. What are the views of the Panel on the design, results, and interpretation of these additional scenario-based exposure simulations?

Sections 5.4.3 included very useful information. It would benefit from a concise summary at the end highlighting the key conclusions and their implications from the exposure estimates previously presented.

9. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the exposure estimates?

All important sources of variability and uncertainty are addressed in the text or extensive tables. The document does a very good job of discussion all potential sources of uncertainty and evaluating the extent to which they can be addressed.

Chapter 7: Characterization of Health Risk Based on Epidemiological Studies

13. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated epidemiology-based risk assessment to be technically sound, appropriately balanced, and clearly communicated?

Overall I found the presentation of the methods clear and well justified. The criteria used to select the epidemiologic studies and metrics used in the risk assessment are well described. The limitations of the approach are also adequately noted.

Commented [AR1]: SV : Jerrett et al. (2009) as the only basis for estimating long-term mortality risks is risky, but it's
the only game in town. This fact should temper confidence in C-R function.

The chapter generally does a good job of describing the results and sensitivity analyses. In general the presentation of results is markedly improved over the prior version. The sequence of results presented in tables and figures for each health endpoint is informative and well described. However some additional editing of the language would further improve clarity. The chapter repeatedly refers to "incidence" or "mortality" when what it is referring to (if my interpretation is correct) are actual counts of deaths or events (epidemiologically incidence and mortality are by definition a proportion or a rate, not a count). In contrast Figure 7-4 does present true mortality estimates (incidence of death). This language needs to be corrected throughout so that counts of deaths are not referred to as incidence. For example, the column headers of Table 7-7 could be modified to "Total number of o3- attributable deaths" and "change in total number of O3 attributable deaths" (if there is a reduction the number should be preceded by a negative sign). Similar language referring to "events" can be used for morbidity tables.

The titles for figures 7-2 and 7-3 are identical.

The section on short term attributable mortality (pg 7-69) indicates that "the mortality risk metric is generally not responsive to meeting the existing and alternative standard levels". It is argued that this occurs because of simulated increases on O3 on some days and regions, even when the standard being met is lower. It is noted that this contrasts with clinical study-based risk estimates. Later in the same section it is noted that "the magnitude of the risk reduction increases as lower alternative standards are simulated". This seems to contradict the previously quoted statement in the same section. Perhaps the initial statement should be modified to indicate that the impact of alternative standards on changes in short term attributable mortality is small but increases as the standard is lower. Then go on to discuss why the impact may be small (this is because of possible increases in ozone in some areas as a result of the way in which meeting the alternative standard was simulated but also because a lot of the attibutable deaths occur at lower levels of the distribution which are not largely impacted by the alternative standards).

It is noted here (and later on in the PA) that based on the approach used to model ozone reductions under alternative standards, ozone levels may actually rise in some areas when meeting lower overall standards. This is because of the dynamics used to model ozone reductions. It should be noted that as a consequence the estimates of the health effects are not precisely the health impacts of reducing ozone to a certain level, but rather the health impact of meeting an alternative standard *through a postulated set of changes to precursors* (some of which results in reductions and some of which result in increases in ozone). This is a subtle but important difference I think. It may be useful to at least note this. Also, is the approach used to model meeting alternative standards (which results in increases in some locations but decreases in others) realistic? The extent to which the simulated increases of O3 at lower standards is realistic and to be expected in the real world needs to be discussed.

14. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources and appropriately characterized the relationship of those sources of uncertainty and variability to the risk estimates?

The discussion of variability and uncertainty covers the main sources of variability and uncertainty and addresses them appropriately to the extent possible with available data. The section also appropriately describes sensitivity analyses that have performed to at least partly assess the plausible impact of some of these uncertainties. The table included is thoughtful, comprehensive, and informative.

15. Adjusting the distributions of O_3 concentrations based on decreasing NOx emissions to just meet the existing and alternative O_3 primary standards resulted, in some cases, in substantial shifts in the spatial and temporal patterns of O_3 across case study urban areas relative to patterns of O_3 that existed for recent air quality, and presumably relative to the patterns present in the study locations of the epidemiology studies from which the concentration response functions were drawn (see section 7.1.1 of the TSD, USEPA,

Commented [AR2]: The estimate of up to approximately 20% of COPD deaths attributed to ozone (7-68) just seems implausible, especially when one considers that the population at risk for dying of COPD is composed of those who are unlikely to exercise and to be outdoors. I know that's what the effect estimate says, but ….

As noted, use of regional effect estimates for long-term exposure risk has dramatic impacts on risk (7-79 and Table 7-14), ranging from 0 to 40% of baseline risk, and 27% in Denver – the latter, as others, seems to stretch plausibility – see first bullet in this section.

Regarding Overall Confidence, in light of the reliance on one study to estimate long-term respiratory mortality effects, and the seemingly large effect estimate, I would have been reluctant to conclude that I had a "reasonable degree of confidence" in these risk estimates (7-86). It also seems inconsistent with the ISA conclusion (ISA 7-31) that there is "limited evidence" for an association between long-term exposure and respiratory mortality, presumably because it is based on only one study.

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Commented [AR3]: SV:
One aspect that is not touched on in discussion of spatial variability in concentrations is the fine scale spatial variability due to roadway gradients

In Table 7-4 on uncertainty analysis, it isn't clear why simulating ozone concentrations for "attainment of both existing and alternative standards" should be included here among other factors assessed in sensitivity analyses. These are simply different ways of expressing impacts of different regulations that provide different insights.

2012). What are the views of the Panel on the characterization of the degree to which these changes in spatial patterns of O_3 introduce uncertainty in risk estimates when effect estimates based on one spatial/temporal pattern of O_3 (the pattern in the epidemiology study) are applied to a substantially different spatial/temporal pattern of O_3 concentrations?

It is noted that the simulations used to estimate Ozone levels under alternative standards result in spatial patterns different than those observed in the epidemiologic studies on which the health effects measures are based. This would result in different health impacts than those predicted from the epidemiologic studies if one or both of the following conditions are met (a) factors associated with space modify the effects of ozone on heath or (b) spatial mobility of persons within the area is a key driver of individual-level exposures. If we are confident that the impact of these two conditions is absent or negligible then we can be confident in the expected health benefits as predicted despite the change in the spatial pattern.

In the absence of a clear rationale for effect modification by space I would argue that the impact of the changing spatial patterns can be ignored. If we believe the effect estimates are capturing the underlying causal effect, then this effect should be approximately generalizable over space.

Commented [AR4]: FM: The uncertainties introduced in risk estimates when effect estimates are based on one spatial/temporal pattern of O3 and are applied to a substantially different spatial/temporal pattern of O3 concentrations are not likely to be any greater than the uncertainties introduced by other factors that are discussed in Chapter 7. Moreover, the central tendency of statistical theory should work to prevent the uncertainties in risk estimates from going only in one direction.

16. In particular, what are the views on the Panel on the characterization of the level of uncertainty associated with estimates of risk associated with days with relatively lower composite (area-wide average) O_3 concentrations and those with relatively higher composite O_3 concentrations?

This is mentioned in the chapter but is not given much relevance. I am not sure there is much more to say about this than what is already included.

Commented [AR5]: SV: This characterization is not based on epidemiology (where the confidence interval around the
effect smooth widens at both extremes) but rather on findings from human experimental and toxicologic findings, which seem to me to pretty sound in this regard.

PA

Chapter 3. Adequacy of the Primary Standard

1. To what extent does section 3.1 (Evidence-based Considerations) capture and appropriately characterize the key aspects of the evidence assessed and integrated in the ISA? To what extent is staff's consideration of the health effects evidence, including the adversity of reported respiratory effects and public health implications technically sound and clearly communicated at an appropriate level of detail? In the Panel's view has the information been appropriately interpreted for the purpose of assessing the adequacy of the current standard?

Overall section 3.1 appropriately describes key aspects of the evidence. I found the

consideration if the evidence to be technically sound, and the information appropriately interpreted for the purpose of assessing the adequacy of the current standard. My main comment is that the section would benefit from synthesis and emphasis of the most important facts relevant to assessing the adequacy of the current standard. There is also some repetition within sections (for example the section on at risks populations repeats the key message several times).

2. With regard to the presentation of the exposure and risk information for the purpose of assessing the adequacy of the current standard, to what extent is the information, including associated limitations and uncertainties, sufficiently characterized, appropriately interpreted and clearly communicated?

Section 3.2 also contains abundant repetitions from the REA and could be synthesized.

The section refers to two important issues in estimating the health impact of alternative standards:

1. It is noted that the simulations used to estimate Ozone levels under alternative standards result in spatial patterns different than those observed in the epidemiologic studies on which the health effects measures are based. This would result in different health impacts than those predicted from the epidemiologic studies if one or both of the following conditions are met (a) factors associated with space modify the effects of ozone on heath or (b) spatial mobility of persons within the area is a key driver of individual-level exposures. If we are confident that the impact of these two conditions is absent or negligible then we can be confident in the expected health benefits as predicted despite the change in the spatial pattern.

2. It is noted that based on the approach used to model ozone reductions under alternative standards, ozone levels may actually rise in some areas when meeting lower overall standards. This is because of the dynamics used to model ozone reductions. It should be noted that as a consequence the estimates of the health effects are not precisely the health impacts of reducing ozone to a certain level, but rather the health impact of meeting an alternative standard *through a postulated set of changes to precursors* (some of which results in reductions and some of which result in increases in ozone). This is a subtle but important difference I think. It may be useful to at least note this. Also, is the approach used to model meeting alternative standards (which results in increases in some locations but decreases in others) realistic?

Pg 3-106 lines 23-28 suggest that since approximately 30-60% of the average daytime O3 is attributable to US anthropogenic sources, then 30-60% of total 03- associated health risks in the urban case studies is attributable to US anthropogenic sources. I don't think this statement is accurate: if the reductions in ozone exposure necessary to eliminate or

sharply reduce ozone associated health effects can be achieved through reductions in US anthropogenic sources alone, then much more than 30-60% in health effects can be attributed to anthropogenic sources.

3. In the Panel's view, does the discussion in section 3.4 provide an appropriate and sufficient rationale to support staff's preliminary conclusion that the current evidence and exposure/risk information call into question the adequacy of the current standard and that it is appropriate to consider revising the standard to achieve additional public health protection?

Overall I though this section was adequate but could benefit from synthesis and emphasis.

Chapter 4. Consideration of Potential Alternative Primary Standards

1. *In the Panel's view, has the evidence and exposure/risk information, including associated limitations and uncertainties, been appropriately characterized and interpreted for the purpose of considering potential alternative standards?*

   Overall I found the chapter to be very well written and to the point. The point regarding ozone serving as an indicator for a standard meant to provide protection against photochemical oxidants is well taken. The discussion regarding averaging times is focused and supported by appropriate evidence. The discussion regarding the form was also very well written. The points supporting he use of an nth highest daily maximum (as opposed to an expected exceedance or percentile-based form) were well stated, however I found the justification of the 4th highest daily max (as opposed to the nth highest) incomplete.

   The section on controlled human exposures studies is an excellent summary although it loses focus in the latter part (pg 4-10 line 19 through pg 4-11 line 6). For example it is not clear why panel studies are discussed here as they are not controlled human exposures studies. The section on page 4-11 lines 6-20 should be consistent with and avid repetitions with pg 4-10 lines 1-18.

   The approach of summarizing associations in cities meeting various alternative standards may be informative but the point of this analysis is not stated clearly and the overall conclusion is not well stated (pg 4-13). What can we conclude then from table 4-1? If studies conducted in areas that have met lower standards do not show an effect do we conclude then that the standard produces appropriate health protection? But if they do does this suggest that an even lower standard is necessary? The logic of this analysis needs to be clarified.

   The subsequent section (on associations below various cutpoints) is clearer but the conclusion could also be summarized more clearly. Is the key point that a

standard of 60 ppb is protective whereas a standard of 65 or 70 is not because studies for which all exposures were below 65-70 still reported associations whereas those at levels below 60 did not? I also found Table 4-2 confusing. The main point needs to be summarized. The reference to the table in the text was confusing.

The section on protection from long term exposures is well done and convincing.

Section 4.4.2.1 would benefit from a final statement of the key conclusions derived from figure 4-1 to 4-4. The same applies to section 4.4.2.2. The bullets are useful but an overall summary statement of what we can conclude from these bullets taken together would be very helpful.

Section 4.4.2.3. The reason for the large difference in the % reduction in mortality associated with meeting a standard of 70 ppb for areas with area wide concentrations > 40ppb and >60ppb is not clear (the footnote does not help clarify). This also applies to other health outcomes. Also the rationale for reporting these two particular estimates is not presented. These types of estimates are repeated later in the chapter so their meaning needs to be clarified.

I'm not sure I would characterize a 9% reduction in ozone associated mortality as a "small " change (pg 4-41 , top of page). In any case it is larger than the effect observed with a standard of 70 ppb so it is not clear why it is considered small.

The chapter also does a reasonable job of grappling and acknowledging the complex issue of uncertainties.

Minor comment: avoid using the word mortality (a rate) when you mean total number of deaths (as in Figure 4-10).

2. *In the Panel's view, does the discussion in section 4.6 provide an appropriate and sufficient rationale, supported by the discussions in sections 4.1 through 4.4, to support staff's preliminary conclusions regarding alternative primary standards (including the indicator, level, averaging time and form) that it is appropriate to consider?*

   The section provides an appropriate and sufficient rationale. Overall he section is very well organized and the arguments are laid out n a clear and compelling way. A few clarifications, particularly of the data presented, would make this an outstanding chapter.

   Tables 4-4 and 4-5 are clear but I found figure 4-13 cryptic. It is not clear exactly what is shown on the Y axis. Is it the ratio of deaths attributable to ozone for alternative standards compared to the 75 ppb standard ? Maybe label the x axis : total ozone attributable deaths, ozone attributable deaths at ozone levels > 20, >40 and >60.

It is difficult to follow the calculations reported on page 4-51 lines 14-21. "For days with area wide concentrations at or above 20ppb a standard with a level of 70…". Is this derived from figure 4-13? But if so isn't this the reduction in deaths attributable to ozone above 20ppb (**not** on days with area wide concentrations at or above 20 ppb??)

3. *Does the Panel have any recommendations regarding additional interpretations and conclusions based on the available information that would be appropriate for consideration beyond those discussed in this chapter?*

   No additional recommendations. Overall this is an excellent chapter. The final section in particular is very well done.